



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US94/05233 <b>(22) International Filing Date:</b> 11 May 1994 (11.05.94)  <b>(30) Priority Data:</b> 08/062,515      14 May 1993 (14.05.93)      US 08/223,932      13 April 1994 (13.04.94)      US  <b>(71) Applicant:</b> WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).  <b>(72) Inventors:</b> LEE, Helen, Tsenwhei; 3625 Fox Hunt, Ann Arbor, MI 48105 (US). PICARD, Joseph, Armand; 5764 Princeton Place, Ypsilanti, MI 48197 (US). SLISKOVIC, Drago, Robert; 4860 Cole Boulevard, Ypsilanti, MI 48197 (US). WIERENGA, Wendell; 1968 Woodlily Court, Ann Arbor, MI 48103 (US).  <b>(74) Agents:</b> ANDERSON, Elizabeth, M.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.		<b>(81) Designated States:</b> AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> N-ACYL SULFAMIC ACID ESTERS (OR THIOESTERS), N-ACYL SULFONAMIDES, AND N-SULFONYL CARBAMIC ACID ESTERS (OR THIOESTERS) AS HYPERCHOLESTEROLEMIC AGENTS		
<b>(57) Abstract</b>  <p>The present invention is directed to compounds useful for the regulation of cholesterol of formula (I), methods for using them and pharmaceutical compositions thereof. In Formula (I) X and Y are oxygen, sulfur, or (CR'R")<sub>n</sub> wherein n is 1 to 4; R is hydrogen, alkyl, or benzyl; R<sub>1</sub> and R<sub>2</sub> are phenyl, substituted phenyl, naphthyl, substituted naphthyl, an aralkyl group, an alkyl chain, adamantyl, or a cycloalkyl group.</p> <div style="text-align: right; margin-right: 100px;"> <math display="block">  \begin{array}{c}  \text{O} \quad \text{O} \\  \parallel \quad \parallel \\  \text{R}_1 - \text{X} - \text{S} - \text{N} - \text{C} - \text{Y} - \text{R}_2 \\  \parallel \quad   \\  \text{O} \quad \text{R}  \end{array}  \quad (I)  </math> </div>		

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N-ACYL SULFAMIC ACID ESTERS (OR THIOESTERS), N-ACYL  
SULFONAMIDES, AND N-SULFONYL CARBAMIC ACID ESTERS (OR  
THIOESTERS) AS HYPERCHOLESTEROLEMIC AGENTS

5           This is a continuation-in-part of United States  
Serial No. 081,062,515 filed May 14, 1993.

BACKGROUND OF INVENTION

10

          This invention relates to chemical compounds  
having pharmacological activity, to pharmaceutical  
compositions which include these compounds, and to a  
pharmaceutical method of treatment. More particularly,  
15       this invention concerns certain N-acyl sulfamic acid  
esters (or thioesters), N-acyl sulfonamides, and  
N-sulfonyl carbamic acid esters (or thioesters) which  
inhibit the enzyme, acyl-coenzyme A:cholesterol  
acyltransferase (ACAT), pharmaceutical compositions  
20       containing these compounds, and a method of treating  
hypercholesterolemia and atherosclerosis.

          The compounds of the instant invention show  
increased chemical stability over those of United  
States Patent No. 5,245,068.

25

          In recent years the role which elevated blood  
plasma levels of cholesterol plays in pathological  
conditions in man has received much attention.  
Deposits of cholesterol in the vascular system have  
been indicated as causative of a variety of  
30       pathological conditions including coronary heart  
disease.

          Initially, studies of this problem were directed  
toward finding therapeutic agents which would be  
effective in lowering total serum cholesterol levels.  
35       It is now known that cholesterol is transported in the  
blood in the form of complex particles consisting of a

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core of cholesteryl esters plus triglycerides and a variety of types of protein which are recognized by specific receptors. For example, cholesterol is carried to the sites of deposit in blood vessels in the form of low density lipoprotein cholesterol (LDL cholesterol) and away from such sites of deposit by high density lipoprotein cholesterol (HDL cholesterol).

Following these discoveries, the search for therapeutic agents which control serum cholesterol turned to finding compounds which are more selective in their action; that is, agents which are effective in elevating the blood serum levels of HDL cholesterol and/or lowering the levels of LDL cholesterol. While such agents are effective in moderating the levels of serum cholesterol, they have little or no effect on controlling the initial absorption of dietary cholesterol in the body through the intestinal wall.

In intestinal mucosal cells, dietary cholesterol is absorbed as free cholesterol which must be esterified by the action of the enzyme, acyl-CoA:cholesterol acyltransferase (ACAT) before it can be packaged into the chylomicrons which are then released into the blood stream. Thus, therapeutic agents which effectively inhibit the action of ACAT prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action.

30

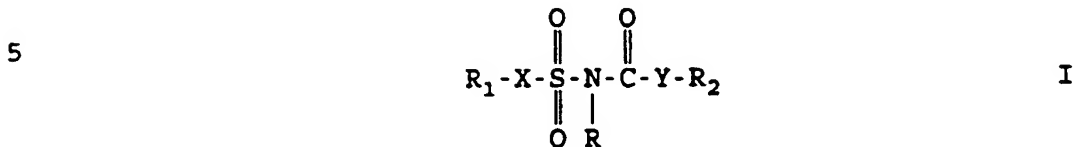
#### SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I below, methods for using the compounds of Formula I, pharmaceutical compositions thereof, and processes for preparing the compounds.

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The first aspect of the invention is a compound of Formula I



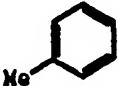
- 10 or a pharmaceutically acceptable salt thereof wherein:  
 X and Y are selected from oxygen, sulfur and  $(\text{CR}'\text{R}'')_n$ ,  
 wherein n is an integer of from 1 to 4 and R' and  
 R'' are each independently hydrogen, alkyl, alkoxy,  
 halogen, hydroxy, acyloxy, cycloalkyl, phenyl  
 15 optionally substituted or R' and R'' together form  
 a spirocycloalkyl or a carbonyl;  
 with the proviso at least one of X and Y is  
 $-(\text{CR}'\text{R}'')_n$ - and with the further proviso when  
 X and Y are both  $(\text{CR}'\text{R}'')_n$  and R' and R'' are  
 20 hydrogen and n is one, R<sub>1</sub> and R<sub>2</sub> are aryl;  
 R is hydrogen, a straight or branched alkyl of from  
 1 to 8 carbon atoms or benzyl;  
 R<sub>1</sub> and R<sub>2</sub> are each independently selected from  
 (a) phenyl or phenoxy each of which is  
 25 unsubstituted or is substituted with 1 to  
 5 substituents selected from  
 phenyl,  
 an alkyl group having from 1 to 6 carbon atoms and  
 which is straight or branched,  
 30 an alkoxy group having from 1 to 6 carbon atoms  
 and which is straight or branched;  
 phenoxy,  
 hydroxy,  
 fluorine,  
 35 chlorine,  
 bromine,  
 nitro,  
 trifluoromethyl,

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- COOH,  
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,  
- (CH<sub>2</sub>)<sub>p</sub>NR<sub>3</sub>R<sub>4</sub> wherein p is zero or one, and each of  
5 R<sub>3</sub> and R<sub>4</sub> is selected from hydrogen or a straight or branched alkyl group having 1 to 4 carbon atoms;  
(b) 1- or 2-naphthyl unsubstituted or substituted with from 1 to 3 substituents selected from  
10 phenyl,  
an alkyl group having from 1 to 6 carbon atoms and which is straight or branched,  
an alkoxy group having from 1 to 6 carbon atoms and which is straight or branched;  
15 hydroxy,  
phenoxy,  
fluorine,  
chlorine,  
bromine,  
20 nitro,  
trifluoromethyl,  
-COOH,  
-COOalkyl wherein alkyl has from 1 to 4 carbon atoms and is straight or branched,  
25 - (CH<sub>2</sub>)<sub>p</sub>NR<sub>3</sub>R<sub>4</sub> wherein p, R<sub>3</sub> and R<sub>4</sub> have the meanings defined above;  
(c) arylalkyl;  
(d) a straight or branched alkyl chain having from 1 to 20 carbon atoms and which is saturated or  
30 contains from 1 to 3 double bonds; or  
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms;  
with the provisos:  
(i) where X is (CH<sub>2</sub>)<sub>n</sub>, Y is oxygen, and R<sub>1</sub> is a  
35 substituted phenyl, then R<sub>2</sub> is a substituted phenyl;

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- (ii) where Y is oxygen, X is  $(CH_2)_n$ ,  $R^2$  is phenyl or naphthyl, then  $R^1$  is not a straight or branched alkyl chain; and
- (iii) the following compounds are excluded:

X	Y	R	$R_1$	$R_2$
$CH_2$	O	H	$(CH_2)_2CH_3$	Ph
$CH_2$	O	H	$CH_3$	Ph
$CH_2$	O	H		i-Pr

Preferred compounds of the instant invention are those of Formula I:

wherein  $R_1$  is phenyl or is phenyl disubstituted in the 2,6-positions,

wherein  $R_2$  is phenyl or is phenyl disubstituted in the 2,6-positions,

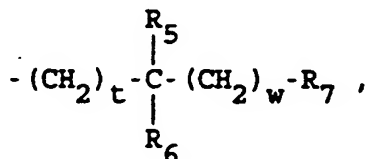
wherein each of  $R_1$  and  $R_2$  is phenyl,

wherein each phenyl is disubstituted in the 2,6-position,

wherein  $R_1$  is phenyl disubstituted in the 2,6-positions and  $R_2$  is phenyl trisubstituted in the 2,4,6-positions,

wherein  $R_1$  is 2,6-bis(1-methylethyl)phenyl and  $R_2$  is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl,

wherein one of  $R_1$  and  $R_2$  is the group



wherein t is zero or 1 to 4; w is zero or 1 to 4 with the proviso that the sum of t and w is not greater than 5;  $R_5$  and  $R_6$  are each independently selected from

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hydrogen or alkyl having from 1 to 6 carbon atoms, or when  $R_5$  is hydrogen,  $R_6$  can be selected from the groups defined for  $R_7$ ; and  $R_7$  is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy, fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or  $-(CH_2)_pNR_3R_4$  wherein P,  $R_3$  and  $R_4$  have the meanings defined above.

Also preferred compounds of the instant invention are those of Formula I wherein  
X is oxygen, sulfur or  $(CR'R'')_n$ ;  
Y is oxygen, sulfur or  $(CR'R'')_n$ , with the proviso that at least one of X or Y is  $(CR'R'')_n$  wherein n is an integer of from 1 to 4 and  $R'$  and  $R''$  are each independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or  $R'$  and  $R''$  taken together form a carbonyl or a spirocycloalkyl group of from 3 to 10 carbons;  
R is hydrogen;  
 $R_1$  is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms;  
 $R_2$  is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, phenoxy optionally substituted with the proviso that only if X is  $(CR'R'')_n$  can  $R_1$  be optionally substituted phenoxy and only if Y is  $(CR'R'')_n$  can  $R_2$  be optionally substituted phenoxy, and with the further proviso that at least one of  $R_1$  and  $R_2$  is optionally substituted phenyl or phenoxy.



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More preferred compounds of the instant invention are those of Formula I wherein

X is oxygen;

Y is  $(CR'R'')_n$  wherein n is an integer of from 1 to 2;

5 R is hydrogen;

R<sub>1</sub> is optionally substituted phenyl;

R<sub>2</sub> is optionally substituted phenyl or phenoxy, straight or branched alkyl of from 1 to 10 carbons, or cycloalkyl of from 3 to 10 carbons;

10 and

R' and R'' are each independently hydrogen, straight or branched alkyl of from 1 to 6 carbons, optionally substituted phenyl, halogen, hydroxy, alkoxy, acyloxy, cycloalkyl, or R' and R'' taken together form a carbonyl or a spirocycloalkyl.

15

The present invention also provides a pharmaceutical composition for regulating plasma cholesterol concentrations comprising a therapeutically effective amount of one or more compounds of Formula I. It further provides a method of treating hypercholesterolemia and for treating atherosclerosis comprising administering to a patient an effective amount of one or more compounds of Formula I with a pharmaceutically acceptable carrier.

20

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#### DETAILED DESCRIPTION OF THE INVENTION

30

The compounds of the present invention provide a novel class of N-acyl sulfamic acid esters (or thioesters), N-acyl sulfonamides, and N-sulfonyl carbamic acid esters (or thioesters) which are ACAT inhibitors, rendering them useful in treating hypercholesterolemia and atherosclerosis.

35

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In Formula I above, illustrative examples of straight or branched saturated hydrocarbon chains having from 1 to 20 carbon atoms include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-undecyl, n-dodecyl, n-hexadecyl, 2,2-dimethyldodecyl, 2-tetradecyl, and n-octadecyl groups.

Illustrative examples of straight or branched hydrocarbon chains having from 1 to 20 carbon atoms and having from 1 to 3 double bonds include ethenyl, 2-propenyl, 2-butenyl, 3-pentenyl, 2-octenyl, 5-nonenyl, 4-undecenyl, 5-heptadecenyl, 3-octadecenyl, 9-octadecenyl, 2,2-dimethyl-11-eicosenyl, 9,12-octadecadienyl, and hexadecenyl.

Straight or branched alkoxy groups having from 1 to 6 carbon atoms include, for example, methoxy, ethoxy, n-propoxy, t-butoxy, and pentyloxy.

Illustrative examples of straight or branched alkyl groups having from 1 to 6 carbon atoms as used in Formula I include methyl, ethyl, n-propyl, isopropyl, n-pentyl, n-butyl, and tert-butyl.

Illustrative examples of cycloalkyl groups, as used in Formula I, include cyclopentyl, cyclohexyl, cyclooctyl, tetrahydronaphthyl, and 1- or 2-adamantyl.

Spirocycloalkyl groups are, for example, spirocyclopropyl, spirocyclobutyl, spirocyclopentyl, and spirocyclohexyl.

Illustrative examples of arylalkyl groups are: benzyl, phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, 2-phenylbutyl, 3-phenylbutyl, benzhydryl, 2,2-diphenylethyl, and 3,3-diphenylpropyl.

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention.

The base salts may be generated from compounds of Formula I by reaction of the latter with one equivalent

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of a suitable nontoxic, pharmaceutically acceptable base followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The compounds of Formula I may be recovered  
5 from the base salt by reaction of the salt with an aqueous solution of a suitable acid such as hydrobromic, hydrochloric, or acetic acid.

Suitable bases for forming base salts of the compounds of this invention include amines such as  
10 triethylamine or dibutylamine, or alkali metal bases and alkaline earth metal bases. Preferred alkali metal hydroxides and alkaline earth metal hydroxides as salt formers are the hydroxides of lithium, sodium, potassium, magnesium, or calcium. The class of bases  
15 suitable for the formation of nontoxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts. See, for example, Berge SN, et al, J Pharm Sci 1977;66:1-19.

20 Suitable acids for forming acid salts of the compounds of this invention containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic,  
25 glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well known in the art.

The compounds of the present invention may also  
30 exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures.

35 Further, the compounds of this invention may exist in unsolvated as well as solvated forms with

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pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

5 Preferred compounds of the present invention are those wherein one of  $R_1$  and  $R_2$  is phenyl, and more preferably wherein one of  $R_1$  and  $R_2$  is substituted phenyl, and still more preferably wherein one of  $R_1$  and  $R_2$  is phenyl disubstituted in the 2,6-positions.

10 In one preferred embodiment both  $R_1$  and  $R_2$  are phenyl disubstituted in the 2,6-positions. In another preferred embodiment  $R_1$  is phenyl disubstituted in the 2,6-position and  $R_2$  is trisubstituted in the 2,4,6-positions.

15 In another preferred embodiment of the present invention,  $R_1$  is 2,6-bis(1-methylethyl)phenyl; and  $R_2$  is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.

20 Preferred compounds of Formula I include, but are not limited to the following:

Sulfamic acid (phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

25 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

30 Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,

Sulfamic acid[adamantaneacetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

35 Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium salt,

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Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)-phenyl ester,

Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,

5        2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl)methyl]sulfonyl]benzeneacetamide,

2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]benzeneacetamide-sodium salt,

10       2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]carbamate,

2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]carbamate-sodium salt,

15       Sulfamic acid (1-oxo-3,3-diphenylpropyl)-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

20       Sulfamic acid [2,6-dichlorophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid trans-[(2-phenylcyclopropyl)-carbonyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

25       Sulfamic acid [2,4,6-trimethoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2,4,6-trimethylphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

30       Sulfamic acid [2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [3-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [2-methoxyphenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,

35       Sulfamic acid (oxophenylacetyl)-2,6-bis(1-methylethyl)phenyl ester,

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- Sulfamic acid [2-trifluoromethylphenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-2-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
5 Sulfamic acid (cyclopentylphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (cyclohexylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (diphenylacetyl)-  
10 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (triphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [(1-phenylcyclopentyl)carbonyl]-  
2,6-bis(1-methylethyl)phenyl ester,  
15 Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-2-phenylbutyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (cyclohexylphenylacetyl)-  
20 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-  
2,6-bis(1-methylethyl)phenyl ester,  
25 Sulfamic acid (1-oxo-3-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)-  
phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [1-oxo-3-[2,4,6-tris(1-methylethyl)-  
30 phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [(acetyloxy)[2,4,6-tris(1-methyl-  
ethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl  
ester,  
Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)-  
35 phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

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Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)-phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,

5 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenoxy]-acetyl]-2,6-bis(1-methylethyl)phenyl ester,

Sulfamic acid [[2,6-bis(1-methylethyl)phenoxy]-acetyl]-2,6-bis(1-methylethyl)phenyl ester, and

10 Sulfamic acid [[2,4,6-tris(1-methylethyl)phenyl]-acetyl]-2,6-bis(phenyl)phenyl ester.

As shown by the data presented below in Table 1, the compounds of the present invention are inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), and are thus effective in inhibiting the esterification and transport of cholesterol across the intestinal cell wall. The compounds of the present invention are thus useful in pharmaceutical formulations for the treatment of hypercholesterolemia or atherosclerosis.

20 The ability of representative compounds of the present invention to inhibit ACAT was measured using an in vitro test more fully described in Field FJ, Salone RG, Biochemica et Biophysica, 1982;712:557-570. The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic acid by measuring the amount of radiolabeled cholesterol oleate formed from radiolabeled oleic acid in a tissue preparation containing rat liver microsomes.

25 The data appear in Table 1 where they are expressed in IC<sub>50</sub> values; i.e., the concentration of test compound required to inhibit the activity of the enzyme by 50%.

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TABLE 1

Example	LAI	
	IC <sub>50</sub>	( $\mu$ M)
5	1	9.7
	2	12
	3	11
	4	13
	5	12
10	6	12
	7	47
	8	21
	10	>5
	11	>10
15	13	25
	14	33
	15	34
	16	36
	17	>50
20	18	22
	19	>50
	20	>50
	21	55
	22	50
25	23	12
	24	26
	25	7.2
	26	28
	27	12
30	28	6
	29	15
	30	4.1
	31	3.3
	32	8.9
	33	9.3



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TABLE 1 (cont.)

	Example	LAI IC <sub>50</sub> ( $\mu$ M)
5	34	7.7
	35	8.9
	36	22
	37	16
	38	31
10	39	32
	40	32
	41	28
	42	7
	43	31
15	44	9.4
	45	5.6
	46	34
	47	38
	48	8.3

20 In one in vivo screen designated APCC, male  
Sprague-Dawley rats (200 to 225 g) were randomly  
divided into treatment groups and dosed at 4 PM with  
either vehicle (CMC/Tween) or suspensions of compounds  
in vehicle. The normal chow diet was then replaced  
25 with a high fat, high cholesterol diet (designated PCC)  
containing 0.5% cholic acid. The rats consumed this  
diet ad libitum during the night and were sacrificed at  
8 AM to obtain blood samples for cholesterol analysis  
using standard procedures. Statistical differences  
30 between mean cholesterol values for the same vehicle  
were determined using analysis of variance followed by  
Fisher's least significant test. The results of this  
trial for representative compounds of the present  
invention appear in Table 2.

35

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TABLE 2

	Compound of Example	% Change (mg/dl)
	1	-63
5	2	-62
	3	-79
	4	-47
	5	-73
	6	-75
10	7	-17
	8	-66
	10	-26
	11	-8
	12	-5
15	13	-31
	14	-12
	15	-14
	16	+10
	17	-40
20	18	-47
	19	-20
	20	-19
	21	-16
	22	-23
25	23	-19
	24	-24
	25	-71
	26	-26
	27	-72
30	28	-30
	29	-9
	30	-40
	31	-30
	32	-48

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TABLE 2 (cont.)

	Example	% Change (mg/dl)
	33	-63
	34	-67
5	35	-9
	36	-6
	37	-50
	38	-16
	39	+5
10	40	-54
	41	-73
	42	-25
	43	-45
	44	-74
15	45	-63
	46	-57
	47	-46
	48	-73

20

In therapeutic use as agents for treating hypercholesterolemia or atherosclerosis, the compounds of Formulas I or II or pharmaceutically acceptable salts thereof are administered to the patient at dosage levels of from 250 to 3000 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 5 to 40 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

30

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For preparing the pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, and cachets.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers are magnesium dicarbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner cachets or transdermal systems are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, or emulsions suitable for oral administration. Aqueous solutions for oral

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administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made  
5 by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethylcellulose, and other suspending agents known to the pharmaceutical formulation art.

10 Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation containing discrete  
15 quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of these packaged forms.

20 Some of the preferred compounds of the present invention are prepared as set forth in Chart I hereof wherein R, R<sub>1</sub> and R<sub>2</sub> have the meanings defined in Formula I; and Z represents a halogen.

In Route 1, a solution of a halide of the  
25 Formula R<sub>2</sub>Z in ether is added to a suspension of Li powder in ether heated under reflux. The solution is cooled to 0°C. The resulting lithium compound is then poured into the liquid ethylene oxide precooled to -78°C. The mixture is allowed to warm up to room  
30 temperature. After work-up with saturated NH<sub>4</sub>Cl, the product (3) is extracted with ethyl acetate. The alcohol (3) is oxidized to the acid (4) by Jones reagent (K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>/H<sub>2</sub>SO<sub>4</sub>) in acetone at 0°C.

Alternatively, the acid (4) can be arrived at  
35 using a method similar to Org. Syn. Coll., 3:557 in which a substituted benzene is chloromethylated

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followed by replacement of the chlorine with nitrile and subsequent hydrolysis of the nitrile to the acid (4).

5 The acid (4) is then allowed to react with oxalyl chloride in toluene at room temperature to give acyl chloride (5). Meanwhile, alcohol (6) is treated with chlorosulfonyl isocyanate in refluxing toluene to give Compound 7, which is then hydrolysed with water to give Compound 8. Compounds 5 and 8 are then mixed in THF in  
10 the presence of  $\text{Et}_3\text{N}$  at room temperature to give Compound 9. In Route 1A, Compound 9 is also obtained by reacting Compound 7 with  $\text{R}_2\text{CH}_2\text{MgZ}$  (15) (commercially available or easily prepared through methods generally known in the art) in THF under reflux. Compound 28 is  
15 obtained by subsequently treating Compound 9 (as arrived at by either Route 1 or 1A) with base and then RZ.

Other compounds of the present invention are prepared as set forth in Chart II (Routes 2 and 3),  
20 hereof wherein R,  $\text{R}_1$  and  $\text{R}_2$  have the meanings defined in Formula I; and Z represents a halogen.

In Route 2, a solution of halide ( $\text{R}_1\text{CH}_2\text{Z}$ ) (14) and thiourea (Compound 24) in absolute ethanol was heated under reflux to give an isothiourea ( $\text{R}_1\text{CH}_2\text{-}$   
25  $\text{S-C(NH)NH}_2$ ) (25). Chlorine gas was bubbled through a suspended solution of the isothiourea in  $\text{H}_2\text{O}$  at  $0^\circ\text{C}$ , followed by  $\text{NH}_3(\text{g})$  to give the sulfonamide ( $\text{R}_1\text{CH}_2\text{SO}_2\text{NH}_2$ ) (18). Condensation between the sulfonamide (18) and an acyl chloride ( $\text{R}_2\text{CH}_2\text{COCl}$ ) (5)  
30 in THF under  $\text{N}_2$  in the presence of  $\text{Et}_3\text{N}$  gives an N-acyl sulfonamide (Compound 21). Compound 18 is also allowed to react with Compound 22 (see Route 3 for preparation of Compound 22) in THF in the presence of  $\text{Et}_3\text{N}$  at room temperature to give Compound 23. Compound 28 is  
35 obtained by subsequently treating Compounds 21 or 23

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(as arrived at by Routes 2 or 3, respectively) with a base and then RZ.

5 The halides RZ,  $R_2Z$ , and  $R_1Z$  used in preparing the compounds of this invention are known in the art or prepared by procedures generally known in the art.

Whereas the preferred compounds of the present invention are prepared as set forth in Charts I and II, it should be understood that the compounds of the present invention can be prepared as set forth  
10 generally as follows.

N-acyl sulfamic acid esters (or thioesters) having the formula of Compound 9 in Chart I Route 1 can be prepared by reacting an acyl chloride and a sulfamate having the formula of Compounds 5 and 8, respectively,  
15 in Route 1. The resulting ester (or thioester) can optionally be reacted with a base, followed by an aryl halide.

Alternatively, N-acyl sulfamic acid esters (or thioesters) having the formula of Compound 9 in Chart I  
20 Route 1A can be prepared by reacting an oxysulfonyl isocyanate and a grignard agent having the formula of Compounds 7 and 15, respectively, in Route 1A. The resulting ester (or thioester) can optionally be reacted with a base, followed by an aryl halide.

25 N-acyl sulfonamides having the formula of Compound 21 in Chart II Route 2 can be prepared by reacting an acid chloride and a sulfonamide having the formula of Compounds 5 and 18, respectively, in Route 2. The resulting sulfonamide can optionally be  
30 reacted with a base, followed by an aryl halide.

N-sulfonyl carbamic acid esters (or thioesters) having the formula of Compound 23 in Chart II Route 3 can be prepared by reacting a sulfonamide and a chloroformate having the formula of Compounds 18  
35 and 22, respectively, in Route 3. The resulting ester

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(or thioester) can optionally be reacted with a base, followed by an aryl halide.

5

## EXAMPLES

The following examples illustrate techniques discovered by the inventors for the preparation of the compounds of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent laboratory techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for this practice. Those of skill in the art should, however, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention. In other words, the following examples are given to illustrate particular compositions and methods within the scope of the present invention and are not intended to limit the scope of the present invention.

25

## EXAMPLE 1

Synthesis of sulfamic acid[(2,6-bis(1-methylethyl)-phenyl)acetyl]-2,6-bis(1-methylethyl)phenyl ester

(a) 2,6-Diisopropylphenylethanol

30

2,6 diisopropylbromobenzene (see J. Org. Chem., 42(14):2426-2431 (1977) for preparation) (30 g, 124.4 mmol) was added to a suspension of Li powder (1.9 g, 273.6 mmol) in ether (100 mL) heated under reflux, the heating was continued for another 4 hours, cooled, and the mixture was poured into ethylene oxide which was precooled to -78°C. The mixture was warmed

35



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slowly to room temperature, saturated  $\text{NH}_4\text{Cl}$  solution was added slowly with caution, the ether layer was separated and washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was evaporated to dryness.

5 After column chromatography (3:1 hexane:ethyl acetate) pure 2,6-diisopropylphenylethanol was obtained (17 g, 66.3%);

NMR ( $\text{CDCl}_3$ ):  $\delta$  1.2-1.3 (m, 12H), 3.05 (t, 2H), 3.15-3.35 (m, 2H), 3.7-3.8 (t, 2H), 7.1-7.3 (m, 3H) ppm.

(b) 2,6-Diisopropylacetic acid

Jones reagent (94 mL, 2 M, 188 mmol) was added to a solution of 2,6-diisopropylphenylethanol (19.2 g, 93.05 mmol) in acetone (600 mL) at  $0^\circ\text{C}$  over 2 hours. The mixture was stirred for another 0.5 hour. The reaction mixture was poured into ether (1 L), washed with brine, and the product was extracted by 1N NaOH. The basic extract was acidified with concentrated HCl, the liberated acid was removed by ether extraction (200 mL  $\times$  5). The combined ether extract was dried over  $\text{MgSO}_4$ , filtered, and then evaporated. The residue was used for the next step without further purification (18.47 g, 90%);

25 NMR ( $\text{CDCl}_3$ ):  $\delta$  1.15-1.35 (m, 12H), 3.05-3.25 (m, 2H), 3.85 (s, 2H), 7.1-7.35 (m, 3H) ppm.

(c) Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-acetyl]-2,6-bis(1-methylethyl)phenyl ester

30 2,6-Diisopropylacetic acid (200 mg, 0.91 mmol) and oxalyl chloride (253.9 mg, 2 mmol) were mixed together in 20 mL of toluene at room temperature under  $\text{N}_2$  with a few drops of DMF as catalyst. The mixture was stirred for 16 hours, the solvent and the excess oxalyl chloride were then removed in vacuo, and the acyl chloride was redissolved in 20 mL of dry THF.

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2,6-Diisopropylphenyl sulfamate (257 mg, 1 mmol, see  
Phos. and Sulf., 19:167 (1984) for preparation) and  
Et<sub>3</sub>N (139  $\mu$ L, 1 mmol) were added to the solution under  
N<sub>2</sub> and the mixture was stirred at room temperature for  
3 hours. The solvent was removed and the residue was  
distributed between ethyl acetate and 1N HCl. The  
organic layer was dried over MgSO<sub>4</sub>, filtered, and  
evaporated, and the pure product was isolated by column  
chromatography (1:1 hexane:EtOAc, 300 mg, 72%),  
mp 166-168°C.

## EXAMPLE 2

Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-  
phenyllacetyl]-2,6-bis(1-methylethyl)phenyl ester  
sodium salt

The sodium salt of the title compound of Example 1  
was prepared by dissolving the title compound of  
Example 1 (1 g, 2.18 mmol) in THF (10 mL), and one  
equivalent of NaH (87 mg, 2.18 mmol) was added to the  
solution and this was then stirred for 0.5 hour. The  
solvent was evaporated and product was obtained by  
trituration with hexane (0.63 g, 60%), mp 242-244°C.

## EXAMPLE 3

Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-  
phenyllacetyl]-2,4,6-tris(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenyl sulfamate was replaced with  
2,4,6-triisopropylphenyl sulfamate, mp 152-155°C.

## EXAMPLE 4

Synthesis of sulfamic acid[adamantaneacetyl]-2,6-bis-  
[1-methylethyl]phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that

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2,6-diisopropylphenylacetyl chloride was replaced with adamantaneacetyl chloride;

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.21 (d, 12H), 1.6-2.0 (m, 15H), 2.15 (s, 2H), 3.4 (m, 2H), 7.15-7.25 (m, 3H) ppm.

5

## EXAMPLE 5

Synthesis of Sulfamic acid[(2,4,6-tris(1-methylethyl)-phenylacetyl)-2,6-bis(1-methylethyl)phenyl ester

(a) 2,4,6-Triisopropylbenzyl alcohol

10 A solution of commercially available 2,4,6-triisopropylbenzoyl chloride (35 g, 131.2 mmol) in 400 mL ether was added slowly to a suspension of lithium aluminum hydride (LAH) (4.89 g, 131.2 mmol) in ether (300 mL) at  $-15^\circ\text{C}$ . The mixture was slowly warmed to  
15 room temperature over 18 hours. Saturated  $\text{Na}_2\text{SO}_4$  solution was added slowly and the ether layer was separated, dried over  $\text{MgSO}_4$ , and evaporated to dryness. The compound was used in the next step without further purification;  
20 NMR ( $\text{CDCl}_3$ ):  $\delta$  1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.3-3.5 (m, 2H), 4.8 (s, 2H), 7.1 (s, 2H) ppm.

(b) 2,4,6-Triisopropylbenzyl bromide

25 A solution of  $\text{PBr}_3$  (2.7 g, 10 mmol) in ether (10 mL) was added slowly to a solution of 2,4,6-triisopropylbenzyl alcohol (4.68 g, 20 mmol) in 20 mL of ether at room temperature. The mixture was stirred for 1 hour, 5 mL of absolute EtOH was added, and stirring was continued for another 0.5 hour. The solvent was  
30 removed and the residue distributed between EtOAc and saturated  $\text{Na}_2\text{CO}_3$ . The EtOAc layer was separated, washed with brine, and dried over  $\text{MgSO}_4$ . The solvent was evaporated and the pure product was isolated by column chromatography (100%  $\text{CH}_2\text{Cl}_2$ , 3.5 g, 59%);  
35 NMR ( $\text{CDCl}_3$ ):  $\delta$  1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.2-3.45 (m, 2H), 4.7 (s, 2H), 7.04 (s, 2H) ppm.

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(c) Sulfamic acid[2,4,6-tris(1-methylethyl)phenyl]-  
acetyl[2,6-bis(1-methylethyl)phenyl ester

A solution of 2,4,6-triisopropylbenzyl bromide (12 g, 40.4 mmol) in dry THF (160 mL) was added to a suspension of Mg powder (1.96 g, 80.8 mmol) (4 hours) in THF (20 mL) heated under reflux. 2,6-Diisopropyl-phenoxy-sulfonyl isocyanate (ROSO<sub>2</sub>NCO) (see Phos. and Sulf., 19:167 (1984) for preparation) (11.45 g, 40.4 mmol) was added neat, and after the addition was completed, the reflux was continued for another 2 hours. The reaction was stirred at room temperature for 16 hours. Saturated NH<sub>4</sub>Cl and EtOAc were added. The EtOAc layer was separated, dried over MgSO<sub>4</sub>, filtered, and evaporated to dryness. After purification by column chromatography (4:1 hexane:EtOAc), the compound was isolated as white solid (13.5 g, 67%), mp 178-180°C.

EXAMPLE 6

20 Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-  
phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester  
sodium salt

This compound was prepared in the same manner as for the title compound of Example 2, except that the title compound of Example 1 was replaced with the title compound of Example 5, mp 250-252°C.

EXAMPLE 7

30 Synthesis of sulfamic acid(phenylacetyl)-2,6-bis-  
(1-methylethyl)phenyl ester

This compound was prepared in the same manner as the title compound of Example 5, except that 2,4,6-triisopropylbenzyl magnesium bromide was replaced with benzylmagnesium chloride (commercially available), mp 150-152°C.

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## EXAMPLE 8

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyllacetyl]-2,4,6-tris(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as the title compound of Example 5, except that 2,6-diisopropylphenoxy sulfonyl isocyanate was replaced with 2,4,6-triisopropylphenoxy sulfonyl isocyanate, mp 178-180°C.

## EXAMPLE 9

Synthesis of 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methylethyl)phenyl]methyl]sulfonyl]benzeneacetamide(a) S-2,4,6-Triisopropylbenzylisothiurea

15 A mixture of 2,4,6-triisopropylbenzyl bromide (6.0 g, 20 mmol) and thiourea (1.536 g, 20.1 mmol) in 180 mL of absolute EtOH was heated under reflux for 3 hours. The reaction was cooled and evaporated. The white powder (7.1 g, 95%) was used for next step without further purification, mp 200-205°C.

(b) 2,4,6-Triisopropylbenzylsulfonamide

20 Chlorine gas was bubbled through a suspension of S-2,4,6-triisopropylbenzylisothiurea hydrobromide (2.5 g, 8.56 mmol) in H<sub>2</sub>O (100 mL) at 0°C for 1 hour. 25 The solid was extracted into EtOAc (50 mL) and NH<sub>3</sub>(g) was bubbled through the EtOAc solution at 0°C for 0.5 hour and the solution was further stirred at room temperature for 2 hours. 2,4,6-Triisopropylbenzyl-sulfonamide was isolated as white powder (100 mg) by 30 column chromatography (4:1 hexane:EtOAc);  
NMR (CDCl<sub>3</sub>): δ 1.2-1.6 (m, 18H), 2.8-3.0 (m, 2H), 3.25-3.4 (m, 2H), 4.75 (s, 2H), 7.0 (s, 2H), ppm.

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(c) 2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris(1-methyl-ethyl)phenyl]methyl]sulfonyl]benzeneacetamide

A solution of 2,4,6-triisopropylbenzylsulfonamide (100 mg, 0.33 mmol), 2,6-diisopropylphenylacetyl chloride (75 mg, 0.34 mmol), and Et<sub>3</sub>N (47  $\mu$ L, 0.34 mmol) in 10 mL THF was stirred at room temperature overnight. The solvent was evaporated and the residue was distributed between ethyl acetate and 0.1N HCl, the organic layer was washed with brine, dried, and evaporated. The pure product (20 mg, 12%) was isolated by column chromatography (4:1 hexane:EtOAc), m/e = 499; NMR (CDCl<sub>3</sub>):  $\delta$  7.05-7.4 (m, 5H), 4.25 (s, 2H), 3.95 (s, 2H), 3.45-3.6 (m, 1H), 3.0-3.15 (m, 2H), 2.85-3.0 (m, 2H), 1.05-1.4 (m, 30H) ppm.

EXAMPLE 10

Synthesis of sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester

This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetyl chloride was replaced with decanoyl chloride, mp 92-94°C.

EXAMPLE 11

Synthesis of sulfamic acid(dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester

This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetyl chloride was replaced with dodecanoyl chloride;

<sup>1</sup>H NMR (DMSO-26):  $\delta$  7.09 (s, 3H), 3.65 (heptet, 2H), 2.05 (t, 2H), 1.48-1.15 (m, 18H); 1.10 (d, 6H), 0.86 (t, 3H) ppm.

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## EXAMPLE 12

Synthesis of sulfamic acid[1-adamantyl(carbonyl)]-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
1-adamantecarboxylic acid, mp 165-167°C.

## EXAMPLE 13

10 Synthesis of sulfamic acid(1-oxo-3,3-diphenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15 3,3-diphenylpropionic acid, mp 149-152°C.

## EXAMPLE 14

Synthesis of sulfamic acid[2,6-dichlorophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
2,6-dichlorophenylacetic acid, mp 203-205°C.

## EXAMPLE 15

25 Synthesis of sulfamic acid trans-[(2-phenylcyclo-  
propyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
30 2,6-diisopropylphenylacetic acid was replaced with  
trans-2-phenylcyclopropylcarboxylic acid, mp 166-168°C.

-30-

## EXAMPLE 16

Synthesis of sulfamic acid[2,5-dimethoxyphenyl-(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetyl chloride was replaced with 2,5-dimethoxyphenylacetyl chloride, mp 150-152°C.

## EXAMPLE 17

10 Synthesis of sulfamic acid[2,4,6-trimethoxyphenyl-(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetic acid was replaced with 2,4,6-trimethoxyphenylacetic acid, mp 159-163°C.

15

## EXAMPLE 18

Synthesis of sulfamic acid[2,4,6-trimethylphenyl-(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetic acid was replaced with 2,4,6-trimethylphenylacetic acid, mp 159-161°C.

## EXAMPLE 19

25 Synthesis of sulfamic acid[2-thiophenyl(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetic acid was replaced with 2-thiopheneacetic acid, mp 133-136°C.

30



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## EXAMPLE 20

Synthesis of sulfamic acid[3-thiophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
3-thiopheneacetic acid, mp 136-138°C.

## EXAMPLE 21

10 Synthesis of sulfamic acid[2-methoxyphenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15 2-methoxyphenylacetic acid, mp 159-161°C.

## EXAMPLE 22

Synthesis of sulfamic acid(oxophenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
benzoylformic acid, mp 106-109°C.

## EXAMPLE 23

25 Synthesis of sulfamic acid[2-trifluoromethylphenyl-  
(acetyl)]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
30 2,6-diisopropylphenylacetic acid was replaced with  
2-trifluoromethylphenylacetic acid, mp 144-149°C.

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## EXAMPLE 24

Synthesis of sulfamic acid(1-oxo-2-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
2-phenylpropionic acid, mp 142-144°C.

## EXAMPLE 25

10 Synthesis of sulfamic acid(cyclopentylphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15  $\alpha$ -phenylcyclopentanecarboxylic acid, mp 142-143°C.

## EXAMPLE 26

Synthesis of sulfamic acid(cyclohexylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
cyclohexylacetic acid;  
 $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35 (s, 1H), 7.1-7.3 (m, 3H),  
25 3.3-3.45 (m, 2H), 2.35 (d, 2H), 1.55-1.95 (m, 8H), 1.22  
(d, 12H), 0.9-1.1 (m, 2H), ppm.

## EXAMPLE 27

30 Synthesis of sulfamic acid(diphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
diphenylacetic acid, mp 164-166°C.

35

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## EXAMPLE 28

Synthesis of sulfamic acid(triphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
triphenylacetic acid, mp 142-144°C.

## EXAMPLE 29

10 Synthesis of sulfamic acid[(1,2,3,4-tetrahydro-  
2-naphthyl)carbonyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15 1,2,3,4-tetrahydro-2-naphthoic acid, mp 137-139°C.

## EXAMPLE 30

Synthesis of sulfamic acid[(1-phenylcyclopentyl)-  
carbonyl]-2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
1-phenyl-1-cyclopentanecarboxylic acid, mp 149-152°C.

## EXAMPLE 31

25 Synthesis of sulfamic acid(3-methyl-1-oxo-  
2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
30 2,6-diisopropylphenylacetic acid was replaced with  
3-methyl-2-phenylvaleric acid;  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.65 (bs, 1H), 7.36-7.11 (m, 8H),  
3.35-3.21 (m, 3H), 2.18 (bs, 1H), 1.73-0.69 (m, 20H),  
ppm.

35

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## EXAMPLE 32

Synthesis of sulfamic acid(1-oxo-2-phenylbutyl)-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetyl chloride was replaced with  
2-phenylbutyryl chloride, mp 142-145°C.

## EXAMPLE 33

10 Synthesis of sulfamic acid(cyclohexylphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15  $\alpha$ -phenylcyclohexanecarboxylic acid, mp 127-137°C.

## EXAMPLE 34

Synthesis of sulfamic acid(1-oxo-2,2-diphenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
2,2-diphenylpropionic acid, mp 140-145°C.

## 25 EXAMPLE 35

Synthesis of sulfamic acid[bis-(4-chlorophenyl)acetyl]-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
30 2,6-diisopropylphenylacetic acid was replaced with  
bis(4-chlorophenyl)acetic acid, mp 175-176°C.

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## EXAMPLE 36

Synthesis of sulfamic acid[(9H-xanthen-9-yl)carbonyl]-  
2,6-bis(1-methylethyl)phenyl ester

5 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
xanthene-9-carboxylic acid, mp 180-181°C.

## EXAMPLE 37

10 Synthesis of sulfamic acid[(9H-fluoren-9-yl)carbonyl]-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
15 9-fluorene-carboxylic acid, mp 146-147°C.

## EXAMPLE 38

Synthesis of sulfamic acid(1-oxo-3-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester

20 This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
hydrocinnamic acid, mp 121-124°C.

## EXAMPLE 39

25 Synthesis of sulfamic acid[bromo(phenyl)acetyl]-  
2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
30 2,6-diisopropylphenylacetic acid was replaced with  
 $\alpha$ -bromophenylacetic acid, mp 155-159°C.

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## EXAMPLE 40

Synthesis of sulfamic acid[1-oxo-3-[2,4,6-tris-  
(1-methylethyl)phenyl]-2-propenyl]-2,6-bis-  
(1-methylethyl)phenyl ester

- 5 (a) 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl  
carboxylic acid, methyl ester

A mixture of methyl acrylate (15.9 mL, 176 mmol) and bis(triphenylphosphine)palladium (II) chloride (0.99 g, 1.4 mmol) in 125 mL dimethylformamide and  
10 125 mL triethylamine was heated to reflux for 1 hour and then 2,4,6-triisopropylbromobenzene (10.0 g, 35 mmol) was added. Reflux was continued for 6 hours and then stirred at room temperature for 16 hours. Partitioned the reaction between water and diethyl  
15 ether. The ether layer was dried with  $\text{MgSO}_4$ , filtered, and concentrated to give a brown oil. Chromatography ( $\text{SiO}_2$ , eluant = 5% ethyl acetate in hexanes) gave 3.80 g of 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester as an off-  
20 white solid, mp 61-63°C.

- (b) 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl  
carboxylic acid

Sodium hydroxide (0.23 g, 5.7 mmol) was added to a  
25 solution of 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester (1.5 g, 5.2 mmol) in 100 mL methanol and 10 mL water. Stirred at room temperature for 48 hours and concentrated to dryness. Partitioned the residue between water and  
30 diethyl ether. The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane. The organic extract was dried over  $\text{MgSO}_4$ , filtered, and concentrated to give 1.33 g of 3-[2,4,6-tris-(1-methylethyl)phenyl]-2-propenyl carboxylic acid as a  
35 white solid, mp 201-203°C.

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(c) Sulfamic acid[1-oxo-3-[2,4,6-tris(1-methylethyl)-phenyl]-2-propenyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as for the title compound of Example 1, except that 2,6-diisopropylphenylacetic acid was replaced with 3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, mp 144-148°C.

EXAMPLE 41

Synthesis of sulfamic acid[1-oxo-3-[2,4,6-tris-(1-methylethyl)phenyl]propyl]-2,6-bis(1-methylethyl)-phenyl ester

(a) 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid, methyl ester

3-[2,4,6-tris(1-methylethyl)phenyl]-2-propenyl carboxylic acid, methyl ester (2.20 g, 7.6 mmol, from Example 40(a)) was dissolved in 100 mL methanol. 0.5 g of 20% palladium on carbon was added and the mixture was charged with 50 psi of hydrogen gas. After 5 hours at room temperature, the reaction was filtered and concentrated to give 2.37 g of 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid, methyl ester as an off-white solid, mp 45-47°C.

(b) 3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid

3-[2,4,6-Tris(1-methylethyl)phenyl]propionic acid, methyl ester (2.12 g, 7.3 mmol) was dissolved in 100 mL methanol and 10 mL water. Sodium hydroxide (0.32 g, 8.0 mmol) was added and the resulting solution was stirred at room temperature for 4 hours. Concentrated in vacuo and partitioned the residue between water and diethyl ether. The aqueous layer was acidified with concentrated HCl and extracted with dichloromethane. The organic extract was dried over MgSO<sub>4</sub>, filtered, and concentrated to give 1.87 g of 3-[2,4,6-tris(1-methyl-

-38-

ethyl)phenyl]propionic acid as a white solid,  
mp 194-196°C.

- 5 (c) Sulfamic acid[1-oxo-3-[2,4,6-tris(1-methylethyl)-  
phenyl]propyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenylacetic acid was replaced with  
3-[2,4,6-tris(1-methylethyl)phenyl]propionic acid,  
10 mp 138-141°C.

#### EXAMPLE 42

- Synthesis of sulfamic acid[(acetyloxy)[2,4,6-tris-  
(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-  
15 phenyl ester

- (a) Acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic  
acid

Glyoxylic acid (1.99 g, 27 mmol) and 1,3,5-triisopropylbenzene (5.0 g, 24.5 mmol) were mixed in 30 mL  
20 glacial acetic acid and 2 mL concentrated sulfuric acid. The resulting solution was heated to reflux for 5 hours and then stirred at room temperature for 16 hours. The reaction mixture was poured into 100 g ice and the resulting mixture was extracted with  
25 diethyl ether. The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated to give an oily solid which was recrystallized from hexanes to give 3.29 g of acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic acid,  
mp 166-169°C.

30

- (b) [(Acetyloxy)[2,4,6-tris(1-methylethyl)phenyl]-  
acetyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
35 2,6-diisopropylphenylacetic acid was replaced with



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acetyloxy[2,4,6-tris(1-methylethyl)phenyl]acetic acid,  
mp 140-146°C.

## EXAMPLE 43

5     Synthesis of sulfamic acid[hydroxy[2,4,6-tris-  
          (1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-  
          phenyl ester

          [(Acetyloxy) [2,4,6-tris(1-methylethyl)phenyl]-  
acetyl]-2,6-bis(1-methylethyl)phenyl ester (1.50 g,  
10     2.7 mmol) was dissolved in 75 mL methanol and 25 mL  
water. Sodium hydroxide (0.22 g, 5.5 mmol) was added  
and the resulting solution was stirred at room  
temperature for 16 hours. Concentrated in vacuo,  
redissolved the residue in water, acidified to pH 4.0  
15     with concentrated HCl and extracted with diethyl ether.  
The organic extract was dried over MgSO<sub>4</sub>, filtered, and  
concentrated to give an oil. Triturated with hexanes  
to give 0.56 g of sulfamic acid [hydroxy[2,4,6-tris-  
(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-  
20     phenyl ester, mp 96-101°C.

## EXAMPLE 44

Synthesis of sulfamic acid[fluoro[2,4,6-tris-  
          (1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)-  
25     phenyl ester

          [Hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-  
2,6-bis(1-methylethyl)phenyl ester (0.73 g, 1.4 mmol)  
was dissolved in 20 mL dichloromethane and added  
dropwise to a solution of diethylaminosulfur  
30     trifluoride (0.19 mL, 1.4 mmol) in 10 mL  
dichloromethane at -8°C. Gradually warmed to room  
temperature and stirred for 16 hours. Concentrated  
in vacuo and partitioned the residue between water and  
ethyl acetate. The organic extract was dried over  
35     MgSO<sub>4</sub>, filtered, and concentrated to give a yellow oil.  
Triturated with hexanes to give 0.39 g of sulfamic acid

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[fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-  
2,6-bis(1-methylethyl)phenyl ester, mp 130-132°C.

## EXAMPLE 45

5 Synthesis of sulfamic acid(3-methyl-1-oxo-2-phenyl-  
pentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt

This compound was prepared in the same manner as  
for the title compound of Example 2, except that the  
title compound of Example 1 was replaced with the title  
10 compound of Example 31, mp 275-277°C.

## EXAMPLE 46

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-  
phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester

15 (a) [2,4,6-tris(1-methylethyl)phenoxy]acetic acid

A solution of 2,4,6-triisopropylphenol (4.0 g,  
18 mmol) in 50 mL tetrahydrofuran was added dropwise to  
a suspension of sodium hydride (1.52 g, 38 mmol) in  
25 mL tetrahydrofuran. The resulting pale green  
20 suspension was stirred for 30 minutes before a solution  
of bromoacetic acid (2.52 g, 18 mmol) in 50 mL  
tetrahydrofuran was added dropwise. The resulting  
thick suspension was stirred for 16 hours and then  
concentrated in vacuo. The residue was partitioned  
25 between 1N HCl and dichloromethane, the organic extract  
was dried over MgSO<sub>4</sub>, filtered, and concentrated to  
give a yellow solid. Recrystallized from hexanes to  
give 3.1 g of [2,4,6-tris(1-methylethyl)phenoxy]acetic  
acid, mp 105-108°C.

30

(b) Sulfamic acid[[2,4,6-tris(1-methylethyl)phenoxy]-  
acetyl]-2,6-bis(1-methylethyl)phenyl ester

This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
35 2,6-diisopropylphenylacetic acid was replaced with

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[2,4,6-tris(1-methylethyl)phenoxy]acetic acid,  
mp 126-128°C.

## EXAMPLE 47

5     Synthesis of sulfamic acid[[2,6-bis(1-methylethyl)-  
phenoxy]acetyl]-2,6-bis(1-methylethyl)phenyl ester

          This compound was prepared in the same manner as  
for the title compound of Example 46, except that  
2,4,6-triisopropylphenol was replaced with  
10     2,6-diisopropylphenol, mp 108-110°C.

## EXAMPLE 48

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-  
phenyl]acetyl]-2,6-bis(phenyl)phenyl ester

15     (a)   2,6-Bis(phenyl)phenyl sulfamate

          A solution of chlorosulfonyl isocyanate (5.57 mL,  
64 mmol) in 50 mL toluene was added dropwise to a  
solution of 2,6-diphenylphenol (15.0 g, 61 mmol) in  
200 mL toluene at 50°C. The resulting white suspension  
20     was heated to reflux for 16 hours. Concentrated  
in vacuo and carefully partitioned the residue between  
water and diethyl ether. The ether layer was dried  
over MgSO<sub>4</sub>, filtered, and concentrated to give an off-  
white solid. Recrystallized from hexanes to give  
25     2,6-bis(phenyl)phenyl sulfamate as a white solid,  
mp 145-147°C.

          (b)   Sulfamic acid[[2,4,6-tris(1-methylethyl)phenyl]-  
acetyl]-2,6-bis(phenyl)phenyl ester

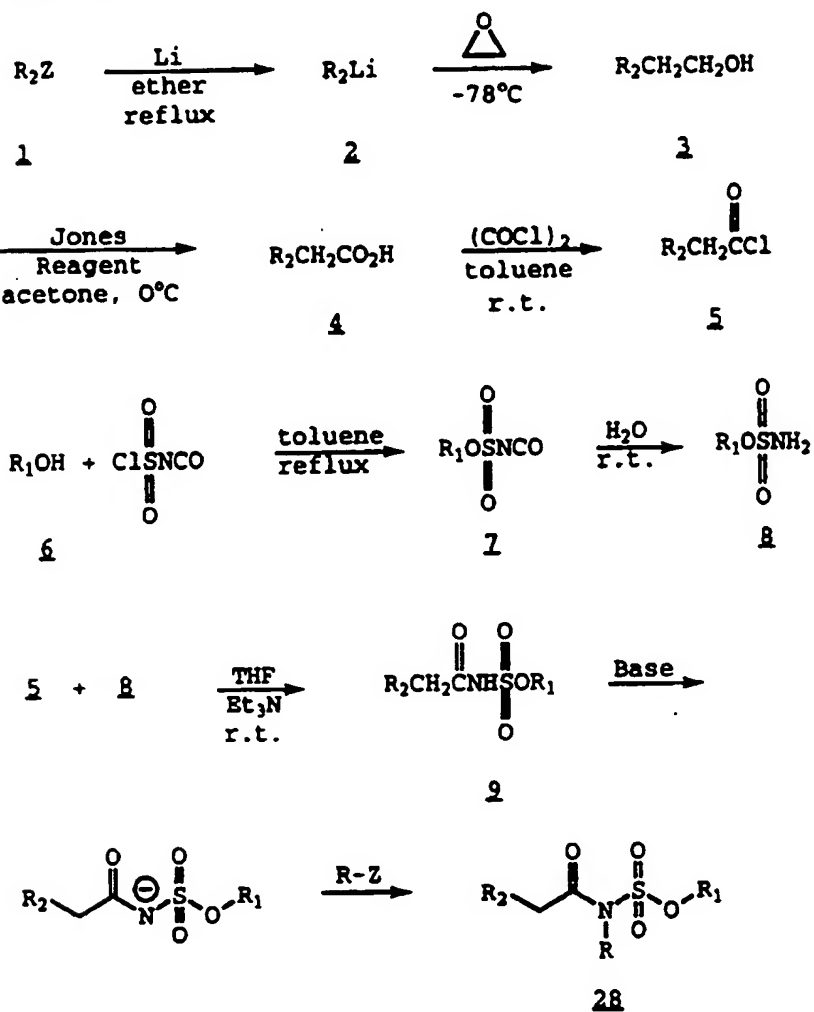
30     This compound was prepared in the same manner as  
for the title compound of Example 1, except that  
2,6-diisopropylphenyl sulfamate was replaced with  
2,6-bis(phenyl)phenyl sulfamate, mp 129-132°C.

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## CHART I

(R, R<sub>1</sub>, and R<sub>2</sub> have the meanings defined in Formula I;  
and Z represents a halogen)

## Route 1

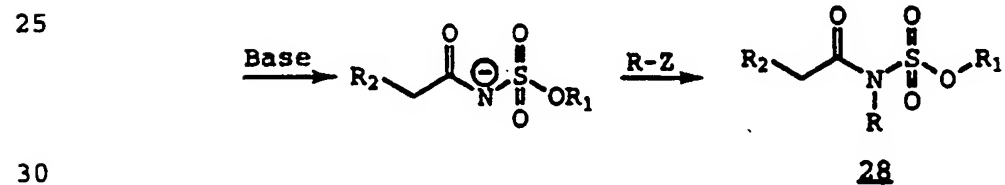
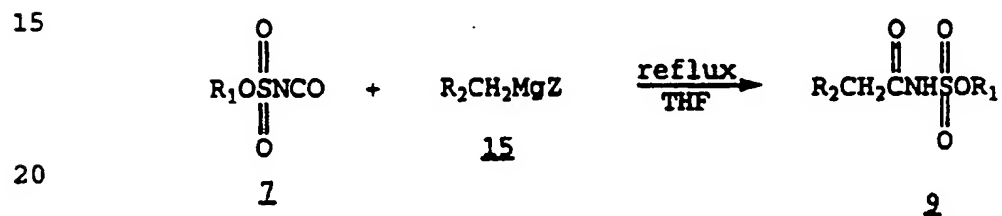
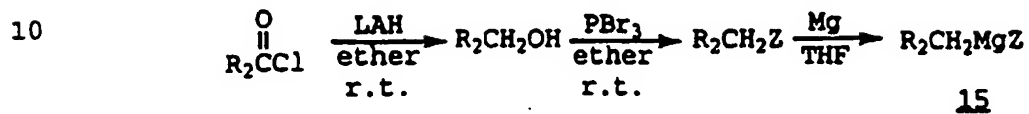


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## CHART I (continued)

(R, R<sub>1</sub>, and R<sub>2</sub> have the meanings defined in Formula I;  
and Z represents a halogen)

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Route 1A

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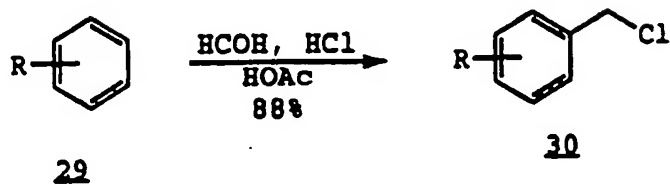
## CHART I (continued)

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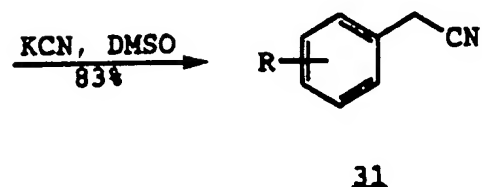
Route 1B

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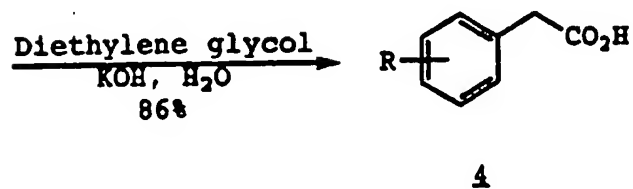
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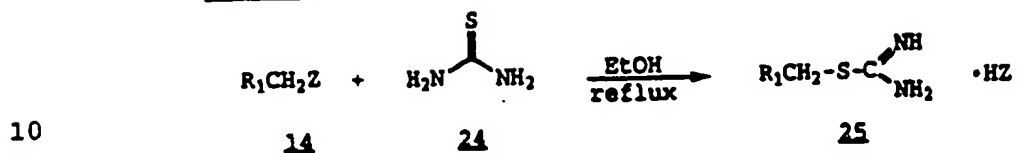
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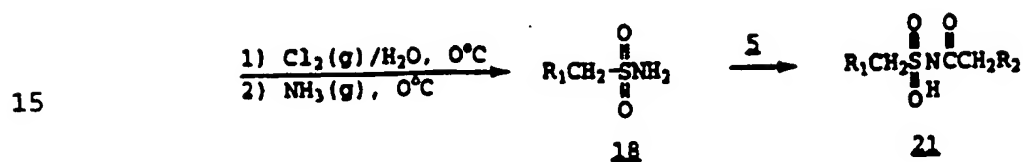
## CHART II

(R, R<sub>1</sub>, and R<sub>2</sub> have the meanings defined in Formula I;  
and Z represents a halogen)

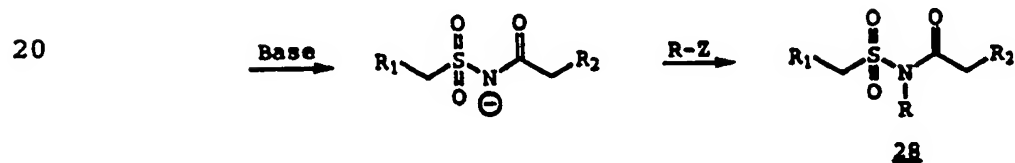
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Route 2

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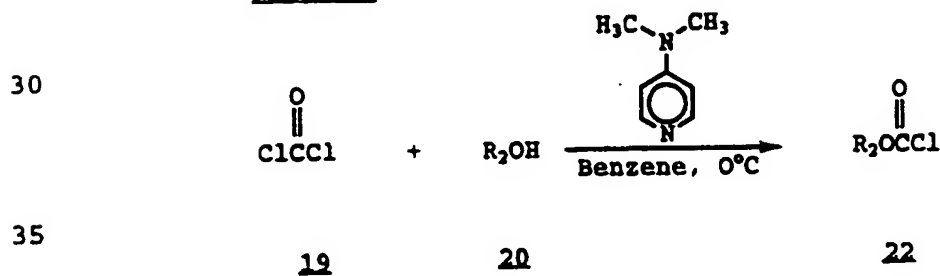


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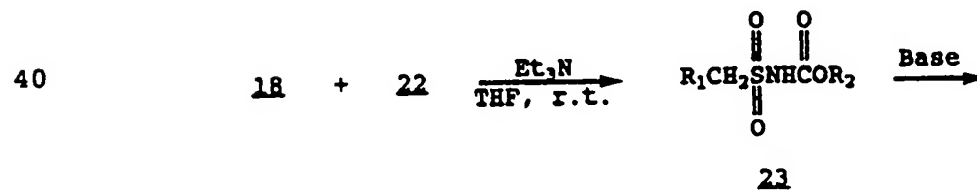
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Route 3

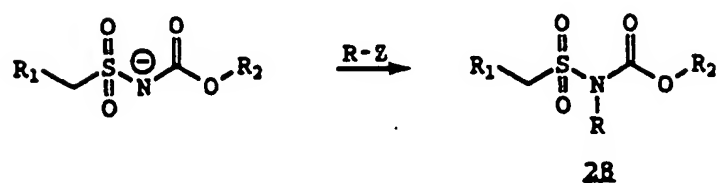
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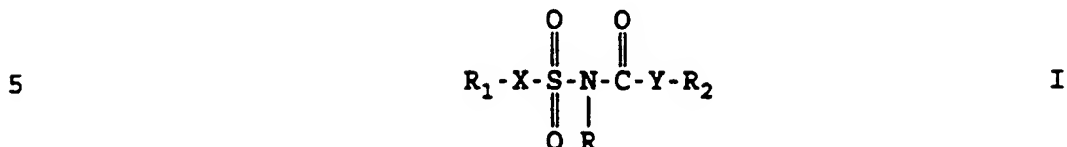


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## CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable salt thereof  
 wherein:

X and Y are selected from oxygen, sulfur and  
 $(\text{CR}'\text{R}'')_n$  wherein n is an integer of from  
 1 to 4 and R' and R'' are each independently  
 hydrogen, alkyl, alkoxy, halogen, hydroxy,  
 15 acyloxy, cycloalkyl, phenyl optionally  
 substituted or R' and R'' together form a  
 spirocycloalkyl or a carbonyl;

with the proviso at least one of X and Y is  
 $(\text{CR}'\text{R}'')_n$  and with the further proviso when  
 20 X and Y are both  $(\text{CR}'\text{R}'')_n$  and R' and R'' are  
 hydrogen and n is one, R<sub>1</sub> and R<sub>2</sub> are aryl;  
 R is hydrogen, a straight or branched alkyl of  
 from 1 to 8 carbon atoms or benzyl;

R<sub>1</sub> and R<sub>2</sub> are each independently selected from  
 25 (a) phenyl or phenoxy each of which is  
 unsubstituted or is substituted with 1 to  
 5 substituents selected from

phenyl,  
 an alkyl group having from 1 to 6 carbon  
 30 atoms and which is straight or branched,  
 an alkoxy group having from 1 to 6 carbon  
 atoms and which is straight or branched;  
 phenoxy,  
 hydroxy,  
 35 fluorine,  
 chlorine,



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- bromine,  
nitro,  
trifluoromethyl,  
40 -COOH,  
-COOalkyl wherein alkyl has from 1 to  
4 carbon atoms and is straight or  
branched,  
- (CH<sub>2</sub>)<sub>p</sub>NR<sub>3</sub>R<sub>4</sub> wherein p is zero or one, and  
45 each of R<sub>3</sub> and R<sub>4</sub> is selected from  
hydrogen or a straight or branched alkyl  
group having 1 to 4 carbon atoms;  
(b) 1- or 2-naphthyl unsubstituted or  
substituted with from 1 to 3 substituents selected  
50 from  
phenyl,  
an alkyl group having from 1 to 6 carbon  
atoms and which is straight or branched,  
an alkoxy group having from 1 to 6 carbon  
55 atoms and which is straight or branched;  
hydroxy,  
phenoxy,  
fluorine,  
chlorine,  
60 bromine,  
nitro,  
trifluoromethyl,  
-COOH,  
-COOalkyl wherein alkyl has from 1 to  
65 4 carbon atoms and is straight or  
branched,  
- (CH<sub>2</sub>)<sub>p</sub>NR<sub>3</sub>R<sub>4</sub> wherein p, R<sub>3</sub> and R<sub>4</sub> have the  
meanings defined above;  
(c) arylalkyl;  
70 (d) a straight or branched alkyl chain  
having from 1 to 20 carbon atoms and which is  
saturated or contains from 1 to 3 double bonds; or

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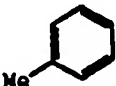
(e) adamantyl or a cycloalkyl group wherein the cycloalkyl moiety has from 3 to 6 carbon atoms;

with the provisos:

(i) where X is  $(CH_2)_n$ , Y is oxygen, and  $R_1$  is a substituted phenyl, then  $R_2$  is a substituted phenyl;

(ii) where Y is oxygen, X is  $(CH_2)_n$ ,  $R^2$  is phenyl or naphthyl, then  $R^1$  is not a straight or branched alkyl chain; and

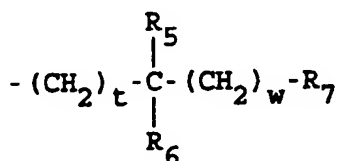
(iii) the following compounds are excluded:

X	Y	R	$R_1$	$R_2$
$CH_2$	O	H	$(CH_2)_2CH_3$	Ph
$CH_2$	O	H	$CH_3$	Ph
$CH_2$	O	H		i-Pr

2. A compound of Claim 1 wherein  $R_1$  is phenyl.
3. A compound of Claim 2 wherein  $R_1$  is phenyl disubstituted in the 2,6-positions.
4. A compound of Claim 1 wherein  $R_2$  is phenyl.
5. A compound of Claim 4 wherein  $R_2$  is phenyl disubstituted in the 2,6-positions.
6. A compound of Claim 1 wherein each of  $R_1$  and  $R_2$  is phenyl.
7. A compound of Claim 6 wherein each phenyl is disubstituted in the 2,6-positions.

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8. A compound of Claim 1 wherein  $R_1$  is phenyl disubstituted in the 2,6-positions and  $R_2$  is phenyl trisubstituted in the 2,4,6-positions.
9. A compound of Claim 1 wherein  $R_1$  is 2,6-bis-(1-methylethyl)phenyl and  $R_2$  is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris(1-methylethyl)phenyl.
10. A compound of Claim 1 wherein  $R_1$  is phenyl or isophenyl disubstituted in the 2,6-positions, wherein  $R_2$  is phenyl or is phenyl disubstituted in the 2,6-positions, wherein each of  $R_1$  and  $R_2$  is phenyl, wherein each phenyl is disubstituted in the 2,6-position, wherein  $R_1$  is phenyl disubstituted in the 2,6-positions and  $R_2$  is phenyl trisubstituted in the 2,4,6-positions, wherein  $R_1$  is 2,6-bis(1-methylethyl)phenyl and  $R_2$  is 2,6-bis(1-methylethyl)phenyl or 2,4,6-tris-(1-methylethyl)phenyl, wherein one of  $R_1$  and  $R_2$  is the group



- wherein  $t$  is zero or 1 to 4;  $w$  is zero or 1 to 4 with the proviso that the sum of  $t$  and  $w$  is not greater than 5;  $R_5$  and  $R_6$  are each independently selected from hydrogen or alkyl having from 1 to 6 carbon atoms, or when  $R_5$  is hydrogen,  $R_6$  can be selected from the groups defined for  $R_7$ ; and  $R_7$  is phenyl or phenyl substituted with from 1 to 3 substituents selected from a straight or branched alkyl group having from 1 to 6 carbon atoms, straight or branched alkoxy group having from 1 to 6 carbon atoms, phenoxy, hydroxy,

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fluorine, chlorine, bromine, nitro, trifluoromethyl, -COOH, COOalkyl wherein alkyl has from 1 to 4 carbon atoms, or  $-(CH_2)_pNR_3R_4$  wherein P,  $R_3$  and  $R_4$  have the meanings defined above.

11. A compound according to Claim 1 wherein

X is oxygen, sulfur or  $(CR'R'')_n$ ;

Y is oxygen, sulfur or  $(CR'R'')_n$  with the proviso that at least one of X or Y is  $(CR'R'')_n$

wherein n is an integer of from 1 to 4 and R'

and R'' are each independently hydrogen,

straight or branched alkyl of from 1 to

6 carbons, optionally substituted phenyl,

halogen, hydroxy, alkoxy, acyloxy,

cycloalkyl, or R' and R'' taken together form

a carbonyl or a spirocycloalkyl group of from 3 to 10 carbons;

R is hydrogen;

$R_1$  is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 10 carbon atoms;

$R_2$  is phenyl optionally substituted, straight or branched alkyl of from 1 to 10 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, phenoxy optionally substituted with the proviso that only if X is  $(CR'R'')_n$  can  $R_1$  be optionally substituted phenoxy and only if Y is  $(CR'R'')_n$  can  $R_2$  be optionally substituted phenoxy, and with the further proviso that at least one of  $R_1$  and  $R_2$  is optionally substituted phenyl or phenoxy.

12. A compound according to Claim 1 wherein

X is oxygen;

Y is  $(CR'R'')_n$  wherein n is an integer of from 1 to 2;

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- 5           R is hydrogen;  
          R<sub>1</sub> is optionally substituted phenyl;  
          R<sub>2</sub> is optionally substituted phenyl or phenoxy,  
              straight or branched alkyl of from 1 to  
              10 carbons, or cycloalkyl of from 3 to  
10           10 carbons;  
          R' and R" are each independently hydrogen,  
              straight or branched alkyl of from 1 to  
              6 carbons, optionally substituted phenyl,  
              halogen, hydroxy, alkoxy, acyloxy,  
15           cycloalkyl, or R' and R" taken together form  
              a carbonyl or a spirocycloalkyl.
13.   A compound named sulfamic acid[[2,4,6-tris-  
      (1-methylethyl)phenyl]acetyl-2,6-bis(1-methyl-  
      ethyl)phenyl ester.
14.   A compound of Claim 1 selected from:  
      Sulfamic acid (phenylacetyl)-2,6-bis-  
      (1-methylethyl)phenyl ester,  
      Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-  
5       acetyl]-2,6-bis(1-methylethyl)phenyl ester,  
      Sulfamic acid [[2,4,6-tris(1-methylethyl)-  
      phenyl]acetyl-2,4,6-tris(1-methylethyl)phenyl  
      ester,  
      Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-  
10       acetyl]-2,4,6-tris(1-methylethyl)phenyl ester,  
      Sulfamic acid[adamantaneacetyl]-2,6-bis-  
      [1-methylethyl)phenyl ester,  
      Sulfamic acid[[2,6-bis(1-methylethyl)phenyl]-  
      acetyl]-2,6-bis(1-methylethyl)phenyl ester-sodium  
15       salt,  
      Sulfamic acid[[2,4,6-tris(1-methylethyl)-  
      phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester-  
      sodium salt,

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- 20 Sulfamic acid (decanoyl)-2,6-bis-(1-methylethyl)phenyl ester,  
Sulfamic acid (dodecanoyl)-2,6-bis-(1-methylethyl)phenyl ester,  
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]benzene-  
25 acetamide,  
2,6-Bis(1-methylethyl)-N-[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]benzene-  
acetamide-sodium salt,  
2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]carbamate,  
30 2,6-Bis(1-methylethyl)phenyl[[[2,4,6-tris-(1-methylethyl)phenyl)methyl]sulfonyl]carbamate-sodium salt,  
Sulfamic acid (1-oxo-3,3-diphenylpropyl)-  
35 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2,6-dichlorophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
40 Sulfamic acid trans-[(2-phenylcyclopropyl)-carbonyl]-2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2,5-dimethoxyphenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2,4,6-trimethoxyphenyl-(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,  
45 Sulfamic acid [2,4,6-trimethylphenyl-(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2-thiophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
50 Sulfamic acid [3-thiophenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2-methoxyphenyl(acetyl)]-  
2,6-bis(1-methylethyl)phenyl ester,

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- Sulfamic acid (oxophenylacetyl)-  
55 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [2-trifluoromethylphenyl-  
(acetyl)]-2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-2-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
60 Sulfamic acid (cyclopentylphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (cyclohexylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (diphenylacetyl)-  
65 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (triphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [(1-phenylcyclopentyl)-  
carbonyl]-2,6-bis(1-methylethyl)phenyl ester,  
70 Sulfamic acid (3-methyl-1-oxo-  
2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl  
ester,  
Sulfamic acid (1-oxo-2-phenylbutyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
75 Sulfamic acid (cyclohexylphenylacetyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-2,2-diphenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [(9H-fluoren-9-yl)carbonyl]-  
80 2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid (1-oxo-3-phenylpropyl)-  
2,6-bis(1-methylethyl)phenyl ester,  
Sulfamic acid [1-oxo-3-[2,4,6-tris-  
(1-methylethyl)phenyl]-2-propenyl]-2,6-bis-  
85 (1-methylethyl)phenyl ester,  
Sulfamic acid [1-oxo-3-[2,4,6-tris-  
(1-methylethyl)phenyl]propyl]-2,6-bis(1-methyl-  
ethyl)phenyl ester,

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- 90 Sulfamic acid [(acetyloxy) [2,4,6-tris-(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [hydroxy[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- 95 Sulfamic acid [fluoro[2,4,6-tris(1-methylethyl)phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid (3-methyl-1-oxo-2-phenylpentyl)-2,6-bis(1-methylethyl)phenyl ester sodium salt,
- 100 Sulfamic acid [(2,4,6-tris(1-methylethyl)-phenoxy)acetyl]-2,6-bis(1-methylethyl)phenyl ester,
- Sulfamic acid [(2,6-bis(1-methylethyl)-phenoxy)acetyl]-2,6-bis(1-methylethyl)phenyl ester, and
- 105 Sulfamic acid [(2,4,6-tris(1-methylethyl)-phenyl)acetyl]-2,6-bis(phenyl)phenyl ester.
- 110 15. A pharmaceutical composition for regulating plasma cholesterol concentrations comprising an effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.
16. A method of treating hypercholesterolemia comprising administering to a patient a therapeutically effective amount of a compound of Claim 1.
17. A method of treating atherosclerosis comprising administering to a patient a therapeutically effective amount of a compound of Claim 1.



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/U 4/05233

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07C307/02 C07C311/51 A61K31/18 A61K31/325

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 39, no. 11, 31 May 1974 Washington, DC, US, pages 1597 - 1600 W.H. DALY, ET AL.: 'Synthesis of alkanesulphonyl isocyanates by thermolysis of trimethylsilylated sulphonyl carbamates' see compounds 4b, 16; table II, compounds with Registry nos. 51003-65-7, 51003-66-7, 46731-59-3, 51003-71-5 ---	1,2
X	EP,A,0 467 183 (BAYER) 22 January 1992 see page 2; example 46 ---	1,2
X	US,A,3 622 626 (G.G.I MOORE) 23 November 1971 see column 1, line 72 ---	1
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

25 July 1994

Date of mailing of the international search report

04.08.94

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 4/05233

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,3 560 563 (S.J. CHILDRESS, et al.) 2 February 1971 see column 1; column 3, line 42; column 4, line 12 ---	1,2
X	US,A,3 377 375 (J.A. STEPHENS) 9 April 1968 see column 1 - column 2; examples II,V,VII,IX,X ---	1,2
X	SYNTHESIS, no. 12, December 1986 Stuttgart, DE, pages 1021 - 1024 W.J. SPILLANE, ET AL.: 'Acylation and sulphonylation of sulphamate esters; synthesis of an acesulfam K precursor' see compound 10 ---	1
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 29, no. 4, July 1992 Provo, US, pages 859 - 866 J. ZINCZUK, ET AL.: 'Intramolecular sulphonamidomethylation. Part II. Fused heterocycles from 2-phenethanesulphonamides' see compound 1n ---	1,2
A	WO,A,92 07826 (WARNER-LAMBERT) 14 May 1992 see page 5 - page 7; claims 1,10 & US,A,5 245 068 (J.A. PICCARD, et al.) cited in the application ---	1,15-17
A	WO,A,92 08692 (WARNER-LAMBERT) 29 May 1992 see page 4 - page 8; claims 1,12 -----	1,15-17

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/05233

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16,17  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 16,17 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Inform. on patent family members

International Application No

PCT/US /05233

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0467183	22-01-92	DE-A- 4023040 JP-A- 4234352	23-01-92 24-08-92
US-A-3622626	23-11-71	NONE	
US-A-3560563	02-02-71	NONE	
US-A-3377375		NONE	
WO-A-9207826	14-05-92	AU-A- 8937091 CA-A- 2093510 EP-A- 0555351 JP-T- 6502415 NZ-A- 240404 US-A- 5245068	26-05-92 01-05-92 18-08-93 17-03-94 25-02-94 14-09-93
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